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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/207,188	12/08/1998	MILAN S. BLAKE	2016-4005US1	6452

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EXAMINER
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ART UNIT	PAPER NUMBER
1645	27

DATE MAILED: 04/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/207,188	Blake et al.
Examiner	**Art Unit**
S. Devi, Ph.D.	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 21, 2003*.

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *73-81 and 83-93* ~~is~~/are pending in the application.

4a) Of the above, claim(s) *73-79* ~~is~~/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *80, 81, and 83-93* ~~is~~/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

RESPONSE TO APPLICANTS' AMENDMENT

Applicants' Amendment

1) Acknowledgment is made of Applicants' amendment filed 01/21/03 (paper no. 26) in response to the non-final Office Action mailed 10/18/02 (paper no. 25).

Status of Claims

2) Claims 80, 89, 90 and 93 have been amended via the amendment filed 01/21/03.

Claims 73-81 and 83-93 are pending in this application.

Claims 80, 81 and 83-93 are under examination.

Prior Citation of Title 35 Sections

3) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

4) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Withdrawn

5) The objection to the specification made in paragraphs 8(a) and 8(b) of the Office Action mailed 10/18/02 (paper no. 25) is withdrawn in light of Applicants' amendment to the specification.

Rejection(s) Withdrawn

6) The rejection of claim 80 made in paragraph 23(a) of the Office Action mailed 10/18/02 (paper no. 25) under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

7) The rejection of claim 80 made in paragraph 23(b) of the Office Action mailed 10/18/02 (paper no. 25) under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

8) The rejection of claim 80 made in paragraph 23(c) of the Office Action mailed 10/18/02 (paper no. 25) under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' arguments. Applicants point to page 11, lines 24-26; and page 12, line 33 through page 13, line 1 of the specification and state that the recited 'protein fragment' is at least 10 amino acids in

length to define a T-cell epitope and is capable of eliciting a T-cell dependent response.

9) The rejection of claims 89, 90 and 93 made in paragraph 23(d) of the Office Action mailed 10/18/02 (paper no. 25) under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

10) The rejection of claims 81 and 83-93 made in paragraph 23(e) of the Office Action mailed 10/18/02 (paper no. 25) under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims and/or the base claim(s).

11) The rejection of claims 89-91 and 93 made in paragraph 24 of the Office Action mailed 10/18/02 (paper no. 25) under 35 § U.S.C. 112, first paragraph, as containing new subject matter, is withdrawn in light of Applicants' amendment to the claims.

Rejection(s) Maintained

12) The rejection of claims 80, 81 and 83-93 made in paragraph 13 of the Office Action mailed 01/11/02 (paper no. 17) and maintained in paragraph 22 of the Office Action mailed 10/18/02 (paper no. 25) under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 26-33 of the U.S. Patent 5,866,135 is maintained for reasons set forth therein.

It is noted that Applicants have agreed to file a terminal disclaimer to overcome the rejection.

13) The rejection of claims 80, 81 and 83-93 made in paragraph 15 of the Office Action mailed 01/11/02 (paper no. 17) and maintained in paragraph 21 of the Office Action mailed 01/11/02 (paper no. 17) under 35 U.S.C § 112, first paragraph, as being non-enabled with regard to the scope, is maintained for reasons set forth therein.

Applicants contend that they have amended the specification on page 25, lines 1-4 to replace 'Figure 6' with --Figure 7--. Applicants state that the description in Example 1, Figure 7 and the Brief Description of the Drawings for Figures 4-9, 'especially with reference to Lancefield's method' enable one skilled in the art 'to perform a bacterial assay'. Applicants assert that the data in Example 1 demonstrate that anti-group A streptococcal polysaccharide antibodies are protective in humans for several group A streptococcus serotypes. Applicants state that Example 7 shows a significant induction of an immunogenic response in rabbits following immunization with the GASP-TT

conjugate. Applicants further make the following statement (see lines 1-3 on page 7 of the amendment filed 01/21/03:

> Applicants have also demonstrated **bactericidal activity** of rabbit serum having high titers of **anti-GASP-TT** antibodies (Example 7). [Emphasis added]

Applicants cite case law and state that FDA approval is not a prerequisite for finding a compound useful within the meaning of the patent laws. Applicants conclude that in view of 'both the human sera and rabbit data', one skilled in the art would reasonably expect the compositions of the invention to be effective to induce protective antibodies in mammals.

Applicants' arguments have been carefully considered, but are non-persuasive. It should be noted that the Office did not raise any issues with regard to the safety of the vaccine. Applicants were not required by the Office to obtain any FDA approval. Figure 7 or Figure 4-9 do not enable one of skill in the art to perform a 'bacterial assay', or to correlate the results of such an assay with 'protection'. The modified Lancefield method is described on page 24, first paragraph, as a bactericidal assay as opposed to a 'bacterial assay'. Furthermore, Applicants' statement that Example 7 describes the "bactericidal activity of rabbit serum having high titers of anti-GASP-TT antibodies" is inaccurate. As clearly set forth in paragraph 21 of the Office Action mailed 01/11/02 (paper no. 17) and contrary to Applicants' assertion, Example 7 is limited to anti-GASP antibody titers as measured by ELISA of sera from rabbits immunized with the native or the unconjugated GASP, a saline solution of a GASP having an assumed molecular weight of about 10 Kd (i.e., n=about 20) and covalently coupled to tetanus toxoid protein, and a GASP conjugate admixed with a clinically acceptable adjuvant, such as aluminum hydroxide or ST, and formula I GASP-protein conjugate admixed in clinically unacceptable adjuvants, such as CFA and IFA. Example 7 is not reflective of the protective nature of GASP conjugate-induced antibodies. It is well known in the art that ELISA antibody titers are not reflective of the bactericidal or protective activity of an antiserum or antibody.

It is re-emphasized that a patent application claiming a method of eliciting a 'protective' immune response in a subject by administration of a conjugate vaccine to a mammal has to necessarily show *in vivo* protective ability of the conjugate vaccine in a mammal, **or** *in vitro* assay results that correlate with *in vivo* protective efficacy of the conjugate vaccine. Contrary to

Applicants' contention, Example 1 of the specification does not teach that antibodies to the polysaccharide of "formula I" wherein n is 3 to 50 are 'protective'. Example 1 shows that Group A streptococcal infection caused by live streptococci induced variable levels of bactericidal group A carbohydrate antibodies in humans infected with these bacteria. Example 1 shows that not all sera from group A streptococcus-infected patients contain a geometric mean group A streptococcal carbohydrate antibody titer of >200,000. Example 1 shows that live whole cell group A streptococci, upon infection in humans, induced a geometric mean bactericidal antibody titer of >200,000 in some infected patients. The specification on page 17, lines 22 and 23, recognizes that such whole cell streptococci are not desirable for use as a vaccine. The infection-induced antibodies in the human sera were induced by the native and non-depolymerized GASP presented to the host immune system on the surface of live whole cells of streptococci. The specification in the last paragraph of page 8 states that a CHO antibody titer of >200,000 (i.e., antibodies induced by group A streptococcal infection) represents 80% killing in the "bacterial assay". However, the specification does not enable one skilled in the art to perform a 'bacterial assay'. The reagents to be used in the 'bacterial assay', steps to be used in the 'bacterial assay' and means of determining the end point of this 'bacterial assay' are neither described, nor are known to those skilled in the art at the time of the instant invention. Moreover, this bacterial assay is described as performed with the sera of humans who were not immunized with the polysaccharide of formula I conjugated to a protein or a protein fragment. The immunogen recited in the instant claims is not live whole cell group A streptococcus, but a polysaccharide of formula I (wherein n is 3 to 50) conjugated to a protein or a protein fragment after modification or treatment of the polysaccharide with several chemicals. In order for formula I polysaccharide-protein conjugate, or formula I polysaccharide-protein fragment conjugate of the instant invention to be used in a method of eliciting a GASP-specific 'protective' immune response in a mammal, the conjugate (**not** the live whole cell Group A streptococci), with or without a clinically acceptable adjuvant, is **required** to induce 'protective' antibodies specific to group A streptococcal polysaccharide, or a geometric mean level of ELISA GASP antibodies in a mammal immunized with the conjugate (as opposed to live whole cell Group A streptococci), which antibody level is correlative of 'protection'. As set forth in paragraph 21 of the Office Action mailed 01/11/02 (paper no. 17), Example 7 and Table IV show that rabbits immunized with the native unconjugated GASP

elicited a geometric mean base line anti-GASP ELISA titer of ≤100 after the first, second and third immunizations. After first immunization, a saline solution of a GASP having an assumed molecular weight of about 10 Kd (i.e., n=about 20) and covalently coupled to tetanus toxoid protein induced the same base line titer of GASP antibodies (i.e., ≤100) in rabbits as that elicited by the uncoupled native GASP. This conjugate in saline elicited measurable GASP antibody titers by ELISA after the second and third immunizations. However, the geometric mean ELISA titer elicited by the conjugate was nowhere near 200,000. Even when rabbits were immunized with this GASP conjugate admixed with a clinically acceptable adjuvant, such as aluminum hydroxide or ST, the geometric mean ELISA titer elicited after three immunizations was nowhere near 200,000. Clearly, the claimed method of eliciting 'protective' antibodies specific to GASP in a mammal by administration of a formula I GASP-protein conjugate wherein n is about 20 (let alone a formula I GASP-protein fragment conjugate), with or without a clinically acceptable adjuvant, is not enabled. Rabbits immunized with the formula I GASP-protein conjugate admixed in clinically unacceptable adjuvants, such as CFA and IFA, elicited a geometric mean ELISA antibody titer that exceeded 200,000 following the second and third immunizations. However, it is important to note that CFA and IFA are not acceptable in the art of vaccines for use in a human or a human child. There is neither any showing, nor is it predictable that one skilled in the art can reproducibly and successfully practice the claimed method using a formula I polysaccharide-protein conjugate or a formula I polysaccharide-protein conjugate wherein n is 3 to 50. Thus, Applicants' own specification provides *prima facie* evidence for lack of enablement for the claimed method. The rejection stands.

Relevant Prior Art

14) The prior art made of record and not currently relied upon in any of the rejections is considered pertinent to Applicants' disclosure:

- Christodoulides *et al.* (*Microbiology* 140: 2951-2960, 1994) expressly taught that ELISA assays, unlike relevant biological assays, are not reliable indicators of protection (see page 2958, left column) against capsulated bacterial pathogen.

Remarks

15) Claims 80, 81 and 83-93 stand rejected.

16) **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicants are reminded of

the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1 (CM1). The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242, which is able to receive transmissions 24 hours a day and 7 days a week. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

18) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

April, 2003

S. DEVI, PH.D.
PRIMARY EXAMINER